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Neural systems for cognitive reappraisal in children and adolescents with autism spectrum disorder

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ABSTRACT

Despite substantial clinical and anecdotal evidence for emotion dysregulation in individuals with autism spectrum disorder (ASD), little is known about the neural substrates underlying this phenomenon. We sought to explore neural mechanisms for cognitive reappraisal in children and adolescents with ASD using functional magnetic resonance imaging (fMRI). We studied 16 youth with ASD and 15 age- and IQ-matched typically developing (TD) comparison youth. Participants were instructed in the use of cognitive reappraisal strategies to increase and decrease their emotional responses to disgusting images. Participants in both groups displayed distinct patterns of brain activity for increasing versus decreasing their emotions. TD participants showed downregulation of bilateral insula and left amygdala on decrease trials, whereas ASD participants showed no modulation of insula and upregulation of left amygdala. Furthermore, TD youth exhibited increased functional connectivity between amygdala and ventrolateral prefrontal cortex compared to ASD participants when downregulating disgust, as well as decreased functional connectivity between amygdala and orbitofrontal cortex. These findings have important implications for our understanding of emotion dysregulation and its treatment in ASD. In particular, the relative lack of prefrontal-amygdala connectivity provides a potential target for treatment-related outcome measurements.

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by a triad of deficits: impairments in reciprocal social interactions, restricted and repetitive patterns of behavior, and delayed or absent communicative skills (APA, 2000). Emotion dysregulation is common in ASD, frequently manifesting as tantrums, meltdowns, or social withdrawal (Laurent and Rubin, 2004). Children with ASD utilize fewer adaptive affect regulation strategies than typically developing (TD) children (Konstantareas and Stewart, 2006), and are more likely to display maladaptive regulation techniques (e.g. avoidance) and less likely to utilize constructive strategies (e.g. cognitive reappraisal; Jahromi et al., 2012). Emotional outbursts in children with ASD exacerbate difficulties in social functioning and are distressing to caregivers (Ozsivadjian et al., 2012). Thus, elucidating mechanisms underlying emotion regulatory processes in ASD is

Abbreviations: ASD, autism spectrum disorder; TD, typically developing.

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important for furthering our understanding of the disorder and may facilitate development of more targeted treatments for emotion dysregulation (Mazefsky et al., 2012).

One emotion regulation strategy that has received substantial attention in the extant scientific literature is cognitive reappraisal, which occurs after production of an emotional response, and includes reinterpretation of an emotion-laden stimulus to modify one's emotional response (Gross, 1998; Gross and Munoz, 1995; Gross and Thompson, 2007; Ochsner and Gross, 2005). Prior studies have extensively addressed neural mechanisms of cognitive reappraisal in healthy adults, suggesting a role for prefrontal and cingulate networks in implementing regulatory processes that in turn modulate activity in limbic regions implicated in emotional experience, including the amygdala (Beauregard et al., 2001; Blair et al., 2007; Kanske et al., 2011; Kim and Hamann, 2007; Levesque et al., 2003; Mak et al., 2009; Ochsner et al., 2004, 2012; Ochsner and Gross, 2007; Phan et al., 2005; Phillips et al., 2008; Urry et al., 2006). In contrast to adults, there are few studies of neural correlates of cognitive reappraisal in TD children and adolescents (Dennis and Hajcak, 2009; Levesque et al., 2004; McRae et al., 2012; Pitskel et al., 2011). Because cognitive behavioral therapy is increasingly used to treat individuals on the ASD spectrum (Danial and Wood, 2013; Sukhodolsky et al., 2013) and cognitive reappraisal skills are a key target of cognitive behavioral therapy approaches (Ball et al., 2013; Goldin et al., 2013; Shurick et al., 2012) we reasoned that a study of the neural correlates of cognitive reappraisal in ASD would be valuable to the field. To our knowledge, no neuroimaging studies to date have employed a cognitive reappraisal paradigm in ASD.

We sought to explore neural mechanisms subserving cognitive reappraisal of disgust in children and adolescents (collectively referred to as youth) with ASD, in comparison to TD youth. We specifically focused on the cognitive reappraisal of disgust for three reasons, two methodological and the other theoretical. First, many of the studies examining cognitive reappraisal have used a range of aversive pictures drawn from the International Affective Picture System (IAPS; Lang et al., 2008). These images can reflect direct threats (human, animal), disgusting images, as well as images reflecting violence and anger. We wanted a thematically homogeneous picture set which would be more likely to engage similar neural circuitry across images. Second, we questioned whether previous work, in attempting to adapt the IAPS images to children, had employed images that were less intense, possibly engaging approach motivation in some children, particularly boys (see McManis et al., 2001). By focusing on disgust we expected we could employ more intense images, which were still acceptable for a child study (i.e., injury or death (adult work) vs. road kill (present study)). Third, disgust images are known to engage insular activity (Chapman and Anderson, 2012) and deficits in functional connectivity of the insula have been specifically implicated in ASD (Ebisch et al., 2011; Uddin and Menon, 2009). In particular, a meta-analytic examination of 24 studies on social information processing and 15 non-social studies (Di Martino et al., 2009) suggested that a distributed system involving the ACC and the anterior insula was hypoactive for individuals with autism. Thus we focused on bilateral insula and amygdala, regions of *a priori* interest because of their implicated roles in processing negative (particularly disgusting) stimuli (Calder et al., 2000; Ibañez et al., 2010; Lane et al., 1997; Phillips et al., 1997; Schafer et al., 2005; Wicker et al., 2003) and emotion regulation (Eippert et al., 2007; Harenski and Hamann, 2006; Kober et al., 2010; Koenigsberg et al., 2010; McRae et al., 2010; Ochsner et al., 2002; Ohira et al., 2006; Schaefer et al., 2002), respectively.

Broadly speaking a large body of data examines the role of amygdala-prefrontal cortex (PFC) function in emotion regulation among typical populations (Zotev et al., 2013). Particularly important for the present study is a growing body of work suggesting atypical PFC-amygdala function in ASD. For instance, some studies suggest reduced vmPFC-amygdala connectivity in ASD (e.g. Swartz et al., 2013). Another group demonstrated reduced resting state functional connectivity between mPFC and both amygdala and insula (von dem Hagen et al., 2013). Conversely, others show greater vmPFC-amygdala functional connectivity (Monk et al., 2010), as well as differential patterns of functional connectivity of the amygdala with a range of cortical regions including the posterior and dorsal cingulate cortex, superior temporal sulcus, and inferior frontal gyrus (Murphy et al., 2012).

We hypothesized that compared to TD youth, those with ASD would exhibit diminished modulation of amygdala and insula during cognitive reappraisal of disgust, and reduced functional connectivity between these regions and prefrontal cortex (PFC).

2. Materials and methods

2.1. Participants

We studied 22 youth with ASD and 24 TD controls. Participants were recruited via local schools, Internet advertising, flyers placed in public locations (campus buildings, libraries), and from the Yale Center for Translational Developmental Neuroscience participant registry. Additionally, participants from past studies who expressed an interest in being considered for future studies were contacted by phone. Individuals were excluded from participation if, by parent report, they had experienced brain injury, brain disease, brain malformation, seizures, epilepsy, hearing or vision loss, motor impairment, or severe allergies. Other exclusion criteria included intellectual disability or learning disability, and, for the typically developing group, parental concern about possible signs of autism or developmental problems, or the presence of a sibling with autism.

Children with ASD were diagnosed via expert clinical judgment supplemented with the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000) and the Autism Diagnostic Interview–Revised (ADI-R; Lord et al., 1994) (Table 1). Experienced personnel administered the Differential Abilities Scale (DAS; Hale and Willis, 2008), a measure of IQ, to all participants. Parents completed the Social Responsiveness Scale (SRS; Constantino and Todd, 2003) assessing their child's behavior. Prior to group analyses, we excluded participants with excessive motion during